Acute Respiratory Distress Syndrome

Definition, Diagnosis, and Routine Management

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KEYWORDS

• Acute respiratory distress syndrome • Heterogeneity • Phenotypes
• Lung-protective ventilation

KEY POINTS

- Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury characterized by severe hypoxemic respiratory failure, bilateral opacities on chest imaging, and low lung compliance.
- ARDS is a heterogeneous syndrome that is the common end point of a wide variety of predisposing conditions, with complex pathophysiology and underlying mechanisms.
- Routine management of ARDS is centered on lung-protective ventilation strategies such as low tidal volume ventilation and targeting low airway pressures to avoid exacerbation of lung injury, as well as a conservative fluid management strategy.
- Advancements in molecular diagnostics and informatics tools may lead to a refined ARDS definition, improved understanding of ARDS heterogeneity and ARDS subphenotypes, and facilitate the development of novel therapeutic approaches.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a rapidly progressive form of acute inflammatory lung injury associated with non-hydrostatic pulmonary edema and severe acute hypoxemic respiratory failure (AHRF).[1] It represents approximately 10% of all intensive care unit (ICU) admissions and 23% of all patients requiring mechanical ventilation.[2] However, clinicians frequently fail to recognize patients with ARDS in clinical practice and implement appropriate treatment strategies.[2] Furthermore, ARDS is a clinically heterogeneous syndrome with complex pathophysiology and underlying

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mechanisms, which has significantly limited the development of simple diagnostic tests or targeted pharmacologic therapies for ARDS that improve patient outcomes.[3] As such, ARDS continues to be associated with high mortality of up to 46% in severe cases.[1,2] The current management strategies for ARDS are largely limited to a few supportive measures that are centered around mechanical ventilation strategies aimed at avoiding further lung injury ("lung-protective ventilation" [LPV]). This article first reviews the current conceptual and clinical definitions of ARDS, current limitations in ARDS definition and diagnosis, and strategies to address those limitations. Then, it reviews the routine management strategies for ARDS, including noninvasive forms of respiratory support, invasive mechanical ventilation (IMV) with LPV strategies, and conservative fluid management.

CURRENT ACUTE RESPIRATORY DISTRESS SYNDROME DEFINITION, LIMITATIONS, AND PROPOSED CHANGES

Acute Respiratory Distress Syndrome Definition

ARDS is conceptually understood as an acute, diffuse, inflammatory lung injury leading to increased pulmonary vascular permeability and non-hydrostatic pulmonary edema, causing loss of aerated lung tissue, increased physiologic dead space, increased lung weight, and decreased lung compliance.[1] ARDS can arise from one of the many risk factors and predisposing conditions, which have historically been divided into "direct" and "indirect" causes of lung injury (**Table 1**).[4,5] Among the potential causes, pneumonia, aspiration of gastric contents, and sepsis are the most common causes of ARDS.[4] These conditions are heterogeneous in nature but eventually lead to the common pathway of acute inflammatory lung injury, resulting in the clinical findings of severe hypoxemic respiratory failure and bilateral pulmonary opacities on chest imaging.[1]

The formal clinical definition of ARDS has been updated several times because the initial description of the syndrome in a case series by Ashbaugh and colleagues.[6] This article focuses on the Berlin definition of ARDS published in 2012 (**Table 2**),[1] whose criteria are retained in the recently published Global Definition of ARDS[7] that builds on the Berlin definition. The Berlin definition was developed to address several limitations of its immediate predecessor, the American-European Consensus Conference (AECC) definition[5] for acute lung injury (ALI), and ARDS. Specifically, the Berlin definition explicitly defined "acute" as a 7-day period following a known clinical insult, required a positive end-expiratory pressure (PEEP) $\geq$5 cmH_2O (or continuous positive airway pressure [CPAP] $\geq$5 cmH_2O for patients with mild ARDS on noninvasive ventilation [NIV]) when evaluating oxygenation, and provided clarifications regarding

Table 1
Risk factors and predisposing conditions for acute respiratory distress syndrome

Direct Lung Injury	Indirect Lung Injury
• Pneumonia (bacterial, viral, or fungal)	•Sepsis from non-pulmonary source
•Aspiration of gastric contents	•Trauma or burn injury
•Toxic inhalational injury	•Pancreatitis
•Near drowning	•Drug overdose
•Pulmonary contusion	•Transfusion of blood products (transfusion-related acute lung injury [TRALI])
	•Cardiopulmonary bypass
	•Reperfusion edema after lung transplantation or embolectomy

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Table 2
The Berlin definition of acute respiratory distress syndrome and mortality rates for different severity categories

Criteria	*Definition*		
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms		
Chest imaging	Bilateral opacities that are not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Hypoxemia		*Mortality (Ranieri et al,[1] 2012)*	*Mortality (Bellani et al,[2] 2016)*
Mild	200 mm Hg < $Pao_2/Fio_2 \leq$ 300 mm Hg with PEEP or CPAP $\geq$ 5 cmH_2O	27%	34.9%
Moderate	100 mm Hg < $Pao_2/Fio_2 \leq$ 200 mm Hg with PEEP $\geq$ 5 cmH_2O	32%	40.3%
Severe	$Pao_2/Fio_2 \leq$ 100 mm Hg with PEEP $\geq$ 5 cmH_2O	45%	46.1%

Abbreviations: CPAP, continuous positive airway pressure; Pao_2/Fio_2, partial pressure arterial oxygen to fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure.

exclusion of hydrostatic edema without the use of pulmonary artery catheters (PACs).[1] It also defined three mutually exclusive severity categories of hypoxemia based on partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2/Fio_2) ratio, with more severe categories of hypoxemia correlating with increased mortality and decreased ventilator-free days (see **Table 2**).[1,2]

Limitations of the Berlin Acute Respiratory Distress Syndrome Definition

Although the Berlin definition of ARDS was developed to address some of the limitations of its predecessors, it is also not without its own shortcomings. First, the Berlin definition requires a patient to receive positive pressure ventilation, undergo arterial blood gas (ABG) sampling, and have either a chest radiograph or computed tomography (CT) performed to satisfy all of its diagnostic criteria. However, such diagnostic and therapeutic modalities may be difficult to obtain for all patients who are at risk of developing ARDS, especially in those who are being treated outside of ICU or in settings with limited resources.[8,9]

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Second, a stated goal of the Berlin definition task force was to improve the reliability of the ARDS definition, particularly the interpretation of chest radiographs for bilateral opacities that has low interobserver reliability even among ARDS experts.[10] However, recent studies continue to demonstrate low interobserver reliability of chest radiograph interpretation for bilateral airspace opacities, which is the main driver of disagreements between physicians when identifying ARDS.[11] Efforts to improve reliability by training physicians and clinical research coordinators with a set of standard chest radiographs developed by the ARDS definition task force were ineffective,[12,13] highlighting the problematic nature of this essential criterion of the ARDS definition.

A third limitation of the Berlin definition is that it encompasses a heterogeneous syndrome with complex pathophysiology and underlying mechanisms and is inherently broad, nonspecific, and imprecise.[3] As a result, there is no standardized, gold-standard diagnostic test for ARDS.[3] The clinical manifestations of ARDS have been correlated with the histopathologic finding of diffuse alveolar damage (DAD) characterized by capillary congestion, pulmonary edema, injury to alveolar lining and endothelial cells, and hyaline membrane formation.[6,14] However, DAD is not the sole pathologic correlate of ARDS and was present in only 45% of patients with ARDS in an autopsy series.[15] Although DAD was more common in patients who met criteria for severe ARDS for more than 72 hours (69%),[15] it was still not a uniform finding, highlighting the clinical and pathologic heterogeneity of ARDS.

Underrecognition of Acute Respiratory Distress Syndrome in Clinical Practice

A related concern about the Berlin definition is that it may be difficult to operationalize at the bedside, resulting in poor recognition of ARDS in clinical practice and failure to administer evidence-based therapies for ARDS.[16] This was most clearly demonstrated in a large international prospective cohort study reporting that only 60% of ARDS cases were recognized by clinicians, with an increase in clinician recognition rates with increasing severity.[2] Moreover, clinician recognition of ARDS at the time of fulfilling ARDS criteria was even lower at 34%, suggesting that ARDS diagnosis was delayed in a substantial proportion of patients.[2] Additional studies have also reported poor clinician recognition rates of ARDS, ranging between 31% and 70%.[17–19]

Missed or delayed diagnoses of ARDS negatively impact the implementation of treatment measures that improve outcomes in ARDS. Several studies have reported overall low adherence to low tidal volume ventilation (LTVV) and substantial delays between ARDS onset and initiation of LTVV, thought to be at least partially due to poor recognition of ARDS.[2,19,20] Clinician recognition of ARDS has been associated with the use of LTVV and higher PEEP, as well as greater use of adjunctive measures such as prone positioning and neuromuscular blockade.[2,19] Therefore, improved methods to facilitate ARDS recognition may be important for timely implementation of appropriate therapies.

Modifications to the Berlin Acute Respiratory Distress Syndrome Definition

To address the concerns regarding the Berlin definition of ARDS, several proposals for modifications have been made. These proposals generally attempt to increase the applicability of the ARDS definition to capture patients who demonstrate clinical features of ARDS but do not strictly satisfy the current Berlin definition or are receiving care in settings where certain diagnostic tests are unavailable. For example, high-flow nasal oxygen (HFNO) has become increasingly popular for treatment of hypoxemic respiratory failure and ARDS since 2012, especially during the recent COVID-

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19 pandemic.[21] However, the low-level positive pressure generated by HFNO is highly variable and cannot reliably satisfy the PEEP requirement of the Berlin definition.[22] In addition, some of the diagnostic testing modalities specified in the Berlin definition, such as ABG and radiographic testing, may not be readily available in settings with limited health care resources.[8,9]

One of the earlier proposals for modifying the Berlin definition, called the Kigali modification,[8] tried to address some of these issues. It proposed.

1. Removal of a PEEP requirement, to allow patients to be diagnosed without positive pressure ventilation
2. An oxygenation cutoff based on oxygen saturation by pulse oximetry (SpO_2) to Fio_2 ratio $\leq$315, in lieu of the Pao_2/Fio_2 ratio that requires ABG testing
3. The use of lung ultrasound as an acceptable imaging modality to assess for bilateral opacities, in addition to plain radiograph and CT.

In the original cohort study conducted in Kigali, Rwanda, these modifications allowed for identification of ARDS in patients who otherwise would not have fully satisfied the Berlin definition yet had severe hypoxemia with a high mortality of 50%.[8] Even in resource-rich settings, the Kigali modification could prove beneficial by facilitating earlier ARDS diagnosis in patients outside of the ICU who are not receiving positive pressure ventilation and avoiding the need for ABG testing and imaging modalities that use ionizing radiation.[9]

More recently, the Global Definition of ARDS[7] was published, which sought to build on the Berlin definition and address similar concerns discussed above. It includes components that are very similar to the Kigali modification, including.

1. Allowing HFNO with a minimum flow rate of 30 L/min, or NIV or CPAP with at least 5 cmH_2O of end-expiratory pressure
2. Allowing either Pao_2/Fio_2 $\leq$300 or SpO_2/Fio_2 $\leq$315 with SpO_2 $\leq$97% to identify hypoxemia
3. Adding ultrasound as a modality of imaging to identify bilateral opacities
4. Not requiring PEEP, oxygen flow, or specific respiratory support devices to diagnose ARDS in resource variable settings.

In both proposed modifications, lung ultrasound can be used to identify bilateral opacities. However, the specific lung ultrasound findings of bilateral opacities have varied across studies. In the Kigali modification, bilateral opacities were identified by ultrasound findings of "B-lines" (an imaging artifact consistent with alveolar-interstitial edema) and/or consolidation without associated effusion in at least one area on each side of the chest.[8] However, a recent study proposed a more detailed, quantitative evaluation method called the lung ultrasound ARDS score that was validated against chest x-ray or CT images when available.[23] This score is calculated based on weighting the presence and type of abnormal ultrasound findings in 12 regions of the chest (six areas in each hemithorax), including the presence of abnormal pleural lines, B-lines, or consolidations.[23] Validation studies of these approaches in prospective studies across diverse populations will be necessary to demonstrate generalizability and standardize the ultrasound examination to support ARDS diagnosis.[24] Additional concerns regarding the use of ultrasound for ARDS diagnosis include inter-operator variability depending on the sonographer's training and external factors that make it difficult to obtain ultrasound images, such as obesity, catheters, and lines.[23,24] Owing to these limitations, the Global Definition of ARDS does not formally include specific ultrasound findings or scoring systems as a part of the definition.[7] Nonetheless, there is growing evidence to support the use of ultrasound for

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identifying bilateral opacities and to promote training in the use of lung ultrasound in evaluating patients with ARDS.[7]

EMERGING APPROACHES FOR IMPROVING THE ACUTE RESPIRATORY DISTRESS SYNDROME DEFINITION AND DIAGNOSIS

The above modifications to the ARDS definition will make it more inclusive and easier to be applied in wider clinical contexts, which may allow for increased inclusion into future epidemiologic studies, clinical research, and clinical trials for ARDS. However, these modifications may also make the ARDS definition more nonspecific and will not address the issues related to poor reliability and heterogeneity of the Berlin definition. Therefore, additional methods spanning molecular diagnostics and informatics domains are being studied to improve the reliability of the Berlin definition and to advance the pathophysiologic understanding of ARDS. Although all of these techniques require additional research before incorporation into a new ARDS definition, they all share a common goal of improving ARDS identification and phenotyping to facilitate earlier delivery of tailored interventions (**Fig. 1**).

Biomarkers for Improving Acute Respiratory Distress Syndrome Identification and Phenotyping

Several candidate biomarkers measured in serum or plasma have been studied for use in improving identification and risk stratification of patients with ARDS (**Table 3**). Measuring several of these biomarkers together may offer better diagnostic and prognostic accuracy than individual biomarkers by themselves, though studies differ with regard to which biomarkers are measured together.[25–27] Although most studies have focused on blood biomarkers, some studies have examined biomarkers from other body compartments, such as protein biomarkers from bronchoalveolar lavage fluid[28–30] and volatile organic compounds in exhaled breath condensates.[31,32] Advanced molecular techniques such as metabolomics[29,33–36] and proteomics[37–39] have also been explored to help identify ARDS and understand the details of its pathophysiology.

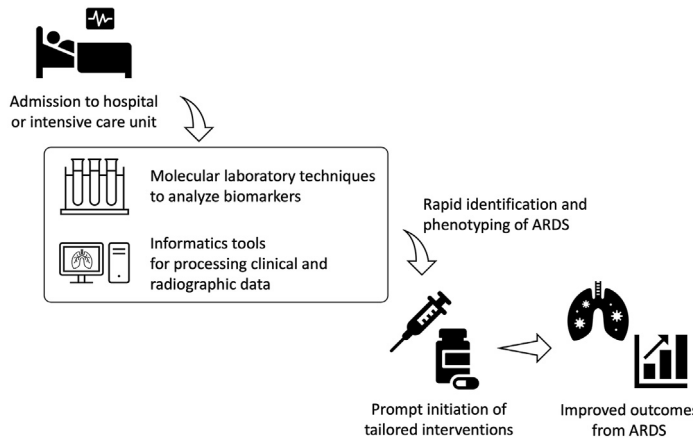

Fig. 1. Clinical and scientific tools being researched to improve identification and phenotyping of acute respiratory distress syndrome (ARDS).

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Biomarkers have also played an important role in understanding the pathophysiologic heterogeneity of ARDS. Earlier studies in this area focused on correlating the biomarker profiles with the clinical risk factors or etiologies of ARDS. For example, surfactant protein-A (SP-A) and surfactant protein-D (SP-D) levels were shown to be higher in patients with ARDS from pneumonia than in patients with ARDS from trauma.[40] Another study demonstrated that von Willebrand factor (vWF) levels were lower in patients with trauma-associated ARDS compared with those with other causes of ARDS and lower in patients with indirect ARDS compared with those with direct ARDS.[41] Angiopoietin-2 (Ang-2) and SP-D were shown to correlate with ARDS from indirect versus direct lung injury, respectively, suggesting distinct mechanisms of lung injury caused by different etiologies of ARDS.[42]

More recently, sophisticated statistical methods analyzing both biomarker and clinical data have been used to divide patients into ARDS subphenotypes, thereby reducing the heterogeneity of patients within the groups. In secondary analyses of several ARDS clinical trials, latent class analysis (LCA) has consistently identified two distinct subphenotypes of ARDS based on clinical and laboratory data.[43–46]

Table 3
Select candidate biomarkers for acute respiratory distress syndrome identification and risk stratification

Biomarker	Mechanistic Involvement in Acute Respiratory Distress Syndrome (ARDS)
Soluble receptor for advanced glycation end products (sRAGE)[25,26,90–92]	Marker of lung epithelial injury. Extracellular domain of multiligand receptor expressed on alveolar type 1 cells and may be a causal intermediate in sepsis-induced ARDS.
Surfactant protein-D (SP-D)[26,40,93,94]	Marker of lung epithelial injury. Synthesized in alveolar type 2 cells and non-ciliated bronchiolar epithelium, involved in lung inflammation.
Angiopoietin-2 (Ang-2)[25,95,96]	Marker of lung endothelial injury. Binds Tie2 receptors on lung endothelial cells and impairs endothelial barrier function.
Von Willebrand factor (vWF)[41,95]	Marker of lung endothelial injury. Glycoprotein involved with hemostasis, released by endothelial cells in endothelial injury.
Soluble intercellular adhesion molecule-1 (sICAM-1)[30,97]	Marker of both lung epithelial and endothelial injury. Expressed on both alveolar epithelial and vascular endothelial cells, involved in neutrophil recruitment into the lung.
Interleukin-6 and interleukin-8[25,98]	Nonspecific pro-inflammatory cytokine.
Tumor necrosis factor-α (TNF-α)[25,98]	Nonspecific pro-inflammatory cytokine.
Soluble tumor necrosis factor receptor (sTNFR)-1 and -2[99]	Binds circulating TNF-α and regulates inflammatory response.
Plasminogen activator inhibitor-1 (PAI-1)[100,101]	Inhibitor of fibrinolysis contributes to fibrin deposition in alveolar spaces.

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One of the two subphenotypes was characterized by elevated levels of inflammatory biomarkers, such as interleukin (IL)-6, IL-8, soluble tumor necrosis factor receptor (sTNFR)-1, and plasminogen activator inhibitor (PAI)-1.[43–46] This subphenotype, labeled the "hyper-inflammatory" phenotype, was consistently associated with higher mortality and worse clinical outcomes compared with the "hypo-inflammatory" phenotype. More strikingly, the hyper-inflammatory subphenotype seemed to benefit significantly from higher PEEP strategy,[43] simvastatin therapy,[44] and liberal fluid strategy,[45] whereas the hypo-inflammatory subphenotype had no benefit or even harm from such therapies. The subphenotypes were subsequently validated in two prospective observational cohorts of ARDS patients, further supporting their generalizability.[47] These results indicate that biomarkers can be informative for identifying ARDS subphenotypes with unique biological characteristics and treatment responses and have the potential to inform future clinical trials.

However, significant challenges still remain in the application of biomarkers in clinical settings. Many biomarker studies show significant variations in patient populations and methodology, making it difficult to establish the optimal timing and method of biomarker measurement. There is also no consensus regarding which biomarker, or panel of biomarkers, most reliably identify ARDS or its subphenotypes. In the studies of LCA-derived ARDS subphenotypes, attempts to develop parsimonious models using just three to five biomarkers and clinical variables (instead of > 30 variables included in the full models) found slightly different sets of biomarkers to be useful for identifying the ARDS subphenotypes.[43,45,46] Moreover, many of the promising biomarkers are not yet available for rapid measurement in clinical laboratories, and the capability to measure the biomarkers in real time still needs to be developed.[44,46] Further research is necessary to standardize the methods and timing of biomarker measurement, validate the reproducibility of biomarker-based ARDS identification and phenotyping across diverse populations, and determine whether personalized treatment strategies based on subphenotypes can indeed improve outcomes.[48]

Informatics Approaches for Improving Reliability of Acute Respiratory Distress Syndrome Recognition

The wealth of clinical data available in electronic medical record (EMR) systems has led to the development of several promising informatics techniques to improve ARDS detection. If deployed, these tools could help to improve the poor recognition of ARDS in clinical practice. Although clinical scores for early identification of ARDS such as the Lung Injury Prediction Score[49] were developed previously, many of its components required manual chart review by clinicians, making it difficult to automate within EMR. Other earlier studies examined automated, rule-based "sniffer" tools that analyzed EMR data to screen patients who may have ARDS, relying primarily on qualifying Pa_{O_2}/Fi_{O_2} ratios and keywords contained in chest imaging reports (such as "bilateral," "infiltrates," and "edema").[50,51] Recent advances in machine learning (ML) and artificial intelligence techniques have led to the further development of sophisticated models that can process a large amount of clinical information to identify ARDS earlier in its course.[52–55] Given the poor reliability of chest imaging interpretation, methods incorporating chest radiographs—such as natural language processing applied to radiology reports[56] and deep convolutional neural network to detect ARDS findings on chest radiograph images[57]—have also been studied with promising results.

Although most informatics tools focus on improving the reliability and timeliness of ARDS identification, they have been used to corroborate the aforementioned hyper- and hypo-inflammatory subphenotypes of ARDS[58,59] as well as to explore a novel

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previously undefined phenotypes of ARDS.[60] These phenotypes demonstrate different treatment responses and distinct clinical characteristics and may have implications for designing and selecting patients for future clinical trials in ARDS.

There are still numerous barriers that need to be overcome before the novel informatics tools for ARDS can be implemented in clinical settings. Most existing studies use retrospective data or secondary analyses of clinical trials, and more prospective studies are needed to validate the model performance and generalizability, especially across different institutions with different patient populations, data recording practices, and/or data processing capabilities.[61] It is also unclear whether the ML model predictions can facilitate meaningful clinical interventions or prevention of ARDS that would not have been possible otherwise,[61] given the rapid onset of ARDS and narrow therapeutic window.[2,62] In addition, the inner workings of the so-called "black-box" algorithms need to be evaluated for their physiologic validity and credibility.[61]

ROUTINE MANAGEMENT STRATEGIES FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Current management strategies for ARDS mainly consist of supportive care, including various modalities of oxygen support and mechanical ventilation strategies designed to reduce further lung injury LPV). Numerous clinical trials of potential ARDS therapies have failed to demonstrate benefit, and no specific pharmacologic therapy currently exists,[3] which is likely explained by the significant clinical and pathophysiologic heterogeneity of patients meeting the current ARDS definition.

Noninvasive Modalities of Oxygen Support

The Berlin definition of ARDS specifies that a patient should be receiving positive pressure ventilation with at least 5 cmH_2O of PEEP to satisfy the definition of ARDS based on the fact that PEEP can markedly affect oxygenation and the Pao_2/Fio_2 ratio.[1] The PEEP requirement could be met during administration of noninvasive positive pressure ventilation (NIPPV) for patients with mild ARDS. HFNO, a newer modality of noninvasive respiratory support that also provides variable levels of PEEP, emerged after the Berlin definition was established. The recent increase in the use of HFNO for treatment of AHRF and ARDS has resulted in the inclusion of HFNO in the new Global Definition of ARDS described above.[7]

However, it is important to note that the benefit of HFNO or NIPPV for improving outcomes from ARDS has not been clearly demonstrated in clinical trials. The results of individual clinical trials of HFNO conducted in various clinical contexts (both before and during the COVID-19 pandemic) have not individually demonstrated a convincing benefit of HFNO therapy, with mixed signals for mortality benefit or intubation rates when compared with standard oxygen therapy or NIPPV.[63–66] A subsequent pooled analyses of these clinical trials and additional studies found potential benefit of HFNO for preventing intubation, but not for reducing mortality.[48] Clinical trials comparing HFNO and NIPPV also have not demonstrated a clear mortality benefit of either treatment modality and have produced somewhat conflicting results for reducing intubation rates.[63,64,67,68] In addition, when the results of several clinical trials comparing conventional oxygen therapy to NIPPV were analyzed for the development of the European Society of Intensive Care Medicine (ESICM) guidelines, there was no significant benefit of NIPPV over conventional therapy for reducing intubation or mortality, leading the guideline committee to not recommend one therapy over the other.[48] Although NIPPV may have a strong physiologic rationale, these potential benefits may

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be countered by its potential harms including poor patient tolerance, impaired ability to clear secretions, increased risk of patient self-induced lung injury, and delayed intubation.[48] NIPPV via helmet interface was also explored as an alternative to the traditional face mask in a small single-center trial,[69] but additional data to support its utility are lacking.

As a consequence, the only affirmative recommendation regarding noninvasive respiratory support in the recent ESICM ARDS guidelines is for using HFNO over conventional oxygen therapy to reduce the risk of intubation (but not to reduce mortality).[48] Otherwise, the ESICM guidelines do not make a recommendation for or against the use of HFNO versus NIPPV or NIPPV versus conventional oxygen therapy.[48] For patients with AHRF or ARDS who are initiated on HFNO therapy, clinical scores such as the respiratory rate-oxygenation index (defined as SpO_2/Fio_2 ratio divided by the respiratory rate) can be helpful for evaluating the risk of HFNO failure and determining whether or not HFNO therapy can be continued.[70,71] However, many patients with ARDS will develop worsening respiratory failure and will ultimately require endotracheal intubation and IMV.

Lung-Protective Ventilation

Once a patient with ARDS is placed on IMV, supportive management is centered on "lung-protective" mechanical ventilation strategies to mitigate several potential mechanisms of ventilator-induced lung injury in ARDS. First, atelectasis and pulmonary edema reduce aerated lung volumes in patients with ARDS. In such cases, even "normal" tidal volumes that may be physiologic for uninjured lungs may nonetheless result in regional overdistention of aerated lung in ARDS and cause "volutrauma."[72] A related mechanism of injury is "barotrauma," which also results from regional lung overdistension (with or without increased airway pressures) and can lead to alveolar rupture, air leaks, and other complications such as pneumothorax and pneumomediastinum.[73] In addition, repetitive opening and closing of alveoli with tidal breaths and the corresponding shearing injury to the lungs may amplify regional lung strain, resulting in "atelectrauma."[73,74] Together, these mechanisms exacerbate and perpetuate lung epithelial and endothelial injury associated with ARDS, which then leads to release of pro-inflammatory mediators and worsening systemic inflammation ("biotrauma").[4,73] As such, mechanical ventilation strategies in ARDS should be optimized to minimize further lung injury.

This is first achieved by ensuring that patients receive low tidal volumes to reduce volutrauma and overdistension injury. In a landmark randomized controlled trial (RCT) from the ARDS network, patients receiving low tidal volume ventilation strategy (initial tidal volume of 6 mL per kg of ideal body weight [IBW] and targeting plateau pressure $\leq$30 cmH_2O) had significantly lower mortality and higher 28-day ventilator-free days compared with those receiving "traditional" tidal volume ventilation strategy (initial tidal volume of 12 mL per kg of IBW and targeting plateau pressure $\leq$50 cmH_2O), causing the trial to be stopped early.[72] Of note, the low tidal volume ventilation group had higher PEEP and Fio_2 requirements as well as more respiratory acidosis than the traditional ventilation group, but nonetheless had greater reductions in plasma IL-6 concentrations, indicating reduced inflammatory response with lower tidal volumes.[72] Based on the results of this trial and analysis of other studies, multiple society guidelines for ARDS all recommend strategies that limit tidal volumes (4–8 mL/kg of IBW) and plateau pressures (<30 cmH_2O).[48,75]

Another important consideration in minimizing further lung injury is using higher PEEP, though the benefits of this strategy are less clearly defined than those of low tidal volume ventilation. Although it was believed that higher PEEP may improve alveolar recruitment and minimize lung injury associated with cyclical alveolar collapse,

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there were also concerns regarding the potential harms of higher PEEP such as lung overdistension and circulatory depression.[74] Three large RCTs did not demonstrate a significant mortality benefit for the higher PEEP strategy, though there were some improvements in oxygenation and other secondary end points with the higher PEEP strategy.[76–78] When the individual patient data from these three trials were pooled in a meta-analysis, there was potential benefit of higher PEEP strategy in patients with moderate or severe ARDS ($Pao_2/Fio_2 \leq 200$ mm Hg), but not in patients with mild ARDS.[74] Secondary analysis of additional clinical trials also did not demonstrate a significant difference in mortality or other clinical outcomes with higher PEEP strategy[75] and using esophageal pressure monitoring (as an estimate of pleural pressure) to guide PEEP titration also did not demonstrate improved outcomes from ARDS compared with empirical high-PEEP strategy.[79] As such, the ideal method for titrating or setting PEEP is not clearly established, and the guidelines do not make clear recommendations for higher PEEP strategy (one guideline with conditional recommendation for higher PEEP strategy and another with no recommendation).[48,75]

Additional studies have suggested that it is not necessarily the PEEP itself, but rather the combined effect of tidal volume and PEEP on airway pressures and lung mechanics that may have a stronger impact on lung injury and clinical outcomes. In a secondary analysis of individual patient data from nine ARDS clinical trials, the driving pressure (defined as the plateau pressure minus PEEP, which is equal to the ratio of tidal volume to respiratory system compliance and is a surrogate for cyclic lung strain with each tidal breath) was examined as an independent variable associated with survival.[80] The study showed that lower driving pressure (indicating lower tidal volume in relation to a given respiratory system compliance) was most strongly associated with survival and that changes in the plateau pressure or PEEP were not individually associated with survival unless they led to a concurrent reduction in the driving pressure. This study provided insight that higher PEEP strategy may be beneficial only if the increased PEEP improves alveolar recruitment and lung mechanics such that the same tidal volume can be delivered with a lower lung strain.[80]

Although the optimal strategy for adjusting ventilator settings in ARDS remains unclear based on available evidence, dynamic adjustment of tidal volume and PEEP to achieve low plateau pressure and perhaps low driving pressure is a reasonable approach. Based on the currently available guidelines,[48,75] a possible starting point would be to set a tidal volume of around 6 mL/kg of IBW (acceptable range 4–8 mL/kg of IBW) and following the protocol for higher PEEP strategy that was used in one of three RCTs mentioned above (ALVEOLI [Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury],[76] LOV [Lung Open Ventilation] Study,[77] EXPRESS [Expiratory Pressure][78]), then monitoring the resulting changes in airway pressures. Subsequently, the ventilator settings should be adjusted incrementally to achieve plateau pressure ≤ 30 cmH_2O and driving pressure ≤ 15 cmH_2O while carefully monitoring for potential complications such as excessive impairments in oxygenation, acid–base balance, or hemodynamics.

Conservative Fluid Strategy

Although it is not explicitly discussed in either of the recent ARDS guidelines, another important supportive measure in ARDS is conservative fluid strategy. Although restricting fluid intake and increasing urinary output are thought to be beneficial for decreasing lung edema and improving clinical outcomes, such strategy may cause decreased cardiac output and worsening of non-pulmonary organ function.[81] This risk–benefit balance was assessed in the FACTT trial,[81] in which patients with ARDS were assigned to either conservative versus liberal fluid strategies and either PAC

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versus central venous catheter in a two-by-two factorial design. The participants' central venous pressure or pulmonary artery occlusion pressure, systemic mean arterial pressure, urine output, and cardiac index were measured to determine their fluid status and prescribe appropriate interventions, consisting of various combinations of fluid, vasopressors, inotropes, and/or diuretics depending on their randomization assignment. Although there was no difference in 60-day mortality between the conservative versus liberal fluid groups, the conservative fluid group had higher 28-day ventilator-free days and ICU-free days, as well as better lung injury scores and oxygenation indexes, without an increase in non-pulmonary organ failures.[81] A subsequent secondary analysis of this trial demonstrated potential differences in treatment responses to fluid strategies between ARDS subphenotypes,[45] but a separate RCT dedicated to evaluating this matter has not been conducted. The exact protocol used in the FACTT trial is difficult to follow, but conservative fluid strategy aimed at reducing fluid intake and increasing urinary output is considered beneficial for improving lung function and is generally preferred in patients with ARDS.

DISCUSSION

This article has focused on the current definition of ARDS and routine management strategies for ARDS that should be applied to nearly all patients with ARDS with only rare exceptions. However, such strategies entail general supportive ventilator management and fluid strategies, rather than targeting a specific ARDS pathophysiologic process. Even adjunctive and rescue therapies for ARDS—such as prone positioning, neuromuscular blockade, corticosteroids, and extracorporeal membrane oxygenation—merely seek to improve oxygenation/ventilation and reduce further lung injury, rather than address the underlying pathologic process. This may explain, at least partially, why mortality from ARDS has not improved significantly in recent years[82] despite some decline noted during the first decade of the 2000s.[83] This stagnation of improvements in ARDS mortality bears some resemblance to the failure of recent RCTs in sepsis[84–86] to replicate the benefits of early goal-directed therapy,[87] highlighting the need for improved recognition of ARDS as well as specific targeted therapies to further improve outcomes.

At the heart of this problem lies the clinical and pathophysiologic heterogeneity of patients meeting the current definition of ARDS. The AECC and Berlin definitions proved useful for establishing a uniform definition of ALI/ARDS and creating a framework for performing many of the practice-informing clinical trials. However, "lumping" different disease processes into a single syndromic definition and then attempting study treatments that target specific pathologic processes has proven exceedingly difficult. This problem has even led to criticisms about the utility and validity of ARDS as a clinical entity, along with suggestions to avoid the term "ARDS" in favor of more specific nomenclature based on concrete pathologic processes (eg, "pneumococcal respiratory distress," or "hypo- vs hyper-inflammatory lung failure").[88,89] In some ways, this is broadly consistent with the recent trends favoring precision medicine approaches in ARDS research, with an increasing focus on "splitting" ARDS into subphenotypes and endotypes that may respond differently to treatments. With the continued advancements in molecular techniques and informatics tools, this approach may lead to a more granular and refined understanding of the heterogeneous syndrome of ARDS. Such efforts could enable opportunities for innovative clinical trial design using prognostic and predictive enrichment to discovery of novel targeted therapies that may move us beyond the routine supportive therapies for ARDS.

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SUMMARY

In summary, ARDS is a severe form of acute inflammatory lung injury that develops secondary to an inciting clinical event, which then leads to non-cardiogenic pulmonary edema, severe hypoxemic respiratory failure, bilateral opacities on chest imaging, and low lung compliance. Despite decades of research, mortality from ARDS remains high, with further improvements in outcomes being hindered by the clinical and pathologic heterogeneity inherent in its syndromic definition, underrecognition in clinical practice, and lack of therapies targeting specific pathologic processes in ARDS. The main treatment strategies for ARDS are supportive measures consisting of noninvasive oxygen support and IMV, LPV strategies, and conservative fluid strategy. The proposed changes to the clinical definition of ARDS, in combination with the advancements in clinical, laboratory, and informatics methods for diagnosing and phenotyping ARDS, may enable innovative approaches to ARDS clinical trials, discovery of novel ARDS therapies, and improvements in clinical outcomes from ARDS.

CLINICS CARE POINTS

- Acute respiratory distress syndrome (ARDS) is currently defined by the Berlin definition, but this definition may soon be updated to allow ARDS to be diagnosed with the use of (1) high-flow nasal oxygen (HFNO), without a requirement for positive end-expiratory pressure (PEEP); (2) SpO_2/Fio_2 criteria to identify hypoxia, without the need for arterial blood gas testing; and (3) ultrasound as an additional modality of imaging to identify bilateral opacities.
- HFNO and noninvasive ventilation are reasonable modalities of oxygen support in patients who are developing ARDS or have mild ARDS, but many patients with ARDS will subsequently require invasive mechanical ventilation.
- Lung-protective ventilation strategy in ARDS consists of delivering low tidal volumes (4–8 mL per kg of ideal body weight) to avoid lung overdistension and optimizing PEEP to promote alveolar recruitment such that plateau and driving pressures, which are surrogate measures of mechanical stress on the lungs, are minimized.
- Conservative fluid strategy should also be applied to ARDS patients to reduce lung edema, by reducing fluid intake and increasing urinary output within safe limits.

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